



## Blastic plasmacytoid dendritic cell neoplasm (BPDCN)

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Find out more about the classification and diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN) and learn more about prognosis and therapy.

### Diagnostic recommendation

Method	Anticoagulant	Recommendation
Cytomorphology	EDTA	mandatory
Immunophenotyping	EDTA or Heparin	mandatory
Chromosome analysis	Heparin	mandatory
FISH	EDTA or Heparin	optional
Molekular genetics	EDTA or Heparin	mandatory



Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare aggressive malignant disease with rapid systemic spread (Swerdlow et al. 2017). The disease occurs mainly in older adults, rarely children are also affected. The latter show milder clinical courses than adults (Jegalian et al. 2010). Blastic plasmacytoid dendritic cell neoplasm accounts for only about 0.4% of all haematological neoplasias (Bueno et al. 2004, Pagano et al. 2013), the exact incidence is unknown, but men are three times more likely to develop the disease than women (Swerdlow et al. 2017).

Most frequent are initially indolent courses with multiple skin lesions. The skin manifestation is sometimes accompanied by a manifestation of lymph nodes or bone marrow involvement. The extent of bone marrow infiltration varies greatly and results in cytopenia, especially thrombocytopenia (Feuillard et al. 2002, Pagano et al. 2013). Rarely do patients show symptoms as in acute leukemia with systemic involvement without skin manifestation (Rauh et al. 2012).

### Classification of Blastic plasmacytoid dendritic cell neoplasm

Formerly assigned to acute leukemias, BPDCN is listed as a separate entity in the new WHO classification 2017. Blastic plasmacytoid dendritic cell neoplasm is associated with a clonal proliferation of immature precursors of plasmacytoid dendritic cells. Whether these are cells of the myeloid or lymphatic series has been controversially discussed for years (Sapienza et al. 2019). Blastic plasmacytoid dendritic cell neoplasm may also occur in association with other myeloid diseases (CMML, MDS and AML) as well as in therapy-associated carcinomas and lymphomas (Swerdlow et al. 2017, Pagano et al. 2013).

### Blastic plasmacytoid dendritic cell neoplasm - Diagnostics

#### Cytomorphology

Characteristic of blastic plasmacytoid dendritic cell neoplasm is a diffuse, monomorphic infiltration of the bone marrow with lympho- or myeloblasts. There are either massive infiltrates or only a slight interstitial infiltration, which can only be detected immunologically. The remaining haematopoiesis, may show dysplastic signs, this is especially true for the megakaryocytes. In case of skin manifestation, there is mainly an infiltration of the dermis with involvement of the subcutaneous fatty tissue. Lymph node infiltrates are found in the interfollicular areas and the medulla.

#### Immunophenotyping

The diagnosis of blastic plasmacytoid dendritic cell neoplasm is mainly based on the immunophenotype. An expression of CD4, CD56, CD123, BDCA-2/CD303 and TCL1 antigens is observed; CD33, CD36 as well as CD2 and CD7 are often co-expressed. Further myeloid and lymphatic markers as well as markers of immature cells are missing. Blastic plasmacytoid dendritic cell neoplasm must be differentially diagnosed from CD56-positive acute myeloid leukemia as well as from extranodal NK/T cell lymphomas, cutaneous T cell lymphomas and subcutaneous panniculitis-like T cell lymphoma.

#### Chromosome analysis

##### Blastic plasmacytoid dendritic cell neoplasm shows no disease-specific genetic changes

Chromosomal aberrations are detected in up to 66% of blastic plasmacytoid dendritic cell neoplasm (Leroux et al. 2002). Hypodiploid or complex aberrant karyotypes with 6 to 8 aberrations are frequently found (Petrella et al. 2005), but no changes specific to the disease are observed. However, the common occurrence of aberrations, which are typically found in myeloid or lymphatic neoplasias, is characteristic in one and the same cell (Leroux et al. 2002).

##### Often loss of chromosomal material due to deletions and unbalanced rearrangements

In a study with a total of 21 patients with blastic plasmacytoid dendritic cell neoplasm, cytogenetic aberrations were detectable in 14 patients (Leroux et al. 2002). A deletion in the long arm of chromosome 5 (5q deletion) was observed in 10 of 14 cases (72%). In 9 out of 14 patients (64%) a deletion in the short arm of chromosome 12 (12p deletion) or a loss of material of chromosome 13 due to a deletion in the long arm (13q deletion) or a monosomy 13 was observed. A deletion in the long arm of chromosome 6 (6q deletion) was found in 7 of 14 patients (50%). A deletion in the long arm of chromosome 15 (15q deletion) or a monosomy 15 was detected in 6 of the 14 patients (43%). In addition, 4 of 14 patients (28%) had monosomy 9 (Leroux et al. 2002).

Array-based copy number analyses (aCGH) confirmed the 12p deletion (12p13, *CDKN1B*) and the 13q loss (13q14.2, *RBT1*; 13q11-q12, *LATS2*) as recurrent aberrations. In addition, deletions were also found in the long arm of chromosome 4 (4q34), in the short arm of chromosome 7 (7p12, *ICZF1*), in the short arm of chromosome 9 (9p21, *CDKN2A/CDKN2B*) and in the short arm of chromosome 17 (17p13, *TP53*) (Dijkman et al. 2007, Jardin et al. 2009, Lucioni et al. 2011). For 9p deletions a prognostic significance has already been demonstrated. Patients with a heterozygous deletion showed a median survival time of 26 months. In contrast, patients with a homozygous 9p deletion were shorter at 11 months and had a lower probability of survival (Lucioni et al. 2011).

##### Recurrent rearrangements in BPDCN affect the *MYC* and the *MYB* gene

In about 10-15% of BPDCN cases, *MYC* rearrangements, which often occur in the context of lymphoid neoplasia, are detectable. However, the translocation partners are usually not immunoglobulin loci (Boddu et al. 2018). In the majority of cases the translocation takes place between 8q24 (*MYC*) and 6p21 (*SUPT3H*), but other translocation partners have also been described with colocalization in the chromosomal bands: 2p12, Xq24, 3p25, and 14q32 (Nakamura et al. 2015, Tzankov et al. 2017, Sumarriva Lezama et al. 2018, Boddu et al. 2018, Sakamoto et al. 2018). The immunohistochemical evidence showed that *MYC* translocations are also associated with *MYC* expression (Sakamoto et al. 2018). Furthermore, there is a strong association between *MYC* rearrangement and immunoblastoid cell morphology. There is evidence that patients with blastic plasmacytoid dendritic cell neoplasm with *MYC* translocation are in median older at diagnosis than patients without *MYC* rearrangement, especially in the presence of t(6;8)(p21;q24) (Sakamoto et al. 2018, Sumarriva Lezama et al. 2018). In a retrospective analysis, a negative influence on therapy response and survival was also demonstrated (Sakamoto et al. 2018). In another small study with 16 BPDCN patients with *MYC*



translocation, 14 of which were already described in the literature, the median survival was 11 months. 11 of the 16 patients had a t(6;8)(p21;q24). In this group the median survival was particularly short at 3 months (Sumarriva Lezama et al. 2018).

As a further recurrent rearrangement in blastic plasmacytoid dendritic cell neoplasm, translocations involving the *MYB* gene (6q23.3) were identified. These appear to occur particularly in the context of pediatric BPDCN, but are also found in adults (Suzuki et al. 2017, Sakamoto et al. 2018). According to the results of the study by Sakamoto et al., rearrangements of the *MYC* and *MYB* genes are mutually exclusive.

## Molecular genetics

### **TET2, ASXL1, NRAS, NPM1 frequently affected by mutations**

Molecular genetic mutations are most frequently detected in the genes *TET2* (36%), *ASXL1* (32%), *NRAS* (20%), *NPM1* (20%), in genes of the *IKAROS* family (20%) and in *ZEB2* (16%) (Menezes et al. 2014). In a study by Menezes et al., patients with mutations in genes involved in DNA methylation (*TET2*, *TET1*, *IDH1*, *IDH2* and *DNMT3A*) showed a shorter survival (11 months mutated vs. 79 months wild type). Patients with mutations in genes coding for transcription factors (*ETV6*, *HOXB9*, *IKAROS* family, *RUNX1*, *ZEB2*) as well as mutations in *TP53* and the *RAS* genes were grouped into a prognostic group. This group also had an unfavourable prognosis (survival 15 months mutant vs. 99 months wild type) (Menezes et al. 2014).

### **Prognosis of Blastic plasmacytoid dendritic cell neoplasm**

Although the majority of patients initially respond to chemotherapy, relapses are very frequent and survival time is short, averaging only 12-14 months (Pagano et al. 2013, Menezes et al. 2014).

### **Therapy of Blastic plasmacytoid dendritic cell neoplasm**

To date, no standardized therapy for blastic plasmacytoid dendritic cell neoplasm has been established. Currently, chemotherapy protocols for both myeloid and lymphatic acute leukemias (in individual cases also analogous lymphoma protocols), possibly followed by allogeneic stem cell transplantation, are used for patients requiring intensive therapy (Aoki et al. 2015, Pagano et al. 2013, Tzankov et al. 2017, Swerdlow et al. 2017). A consolidating autologous stem cell transplantation also seems promising (Aoki et al. 2015).

Targeted approaches could expand the therapeutic arsenal for blastic plasmacytoid dendritic cell neoplasm in the future. For example, the interleukin-3 receptor (CD123) is a suitable target due to its overexpression. Tagraxofusp, a fusion protein consisting of diphtheria toxin coupled to IL3 (Frankel et al. 2014), was approved by the FDA (FDA press release 2018) after a Phase II study and also holds the European marketing authorization for the treatment of BPDCN since January 2021 (EMA 2021). Under therapy with Tagraxofusp, response rates of 90% in previously untreated blastic plasmacytoid dendritic cell neoplasm and 67% in patients with previous therapy were achieved (Pemmaraju et al. 2019).

Gene expression and immunohistochemical analyses have shown an aberrant activation of the NF- $\kappa$ B signaling pathway in blastic plasmacytoid dendritic cell neoplasm. These genes, as already successfully tested *ex vivo* and in the xenograft mouse model, could represent a further target structure for specific therapies in the future (Sapienza et al. 2014, Phillippe et al. 2017).

In addition, hypomethylating agents as well as BET inhibitors are currently in preclinical testing (Ceribelli et al. 2016, Emadali et al. 2016, Sapienza et al. Cancer 2019 and Haematologica 2019, Lezama & Ohgami 2019), and the use of the BCL2 inhibitor Venetoclax is also being evaluated in a clinical phase I study (NCT03485547).

## References

You can find the corresponding references here:

<https://www.mll.com/en/diagnostic-offer/others/blastic-plasmacytoid-dendritic-cell-neoplasm-bpdcn.html#references>